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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,648	12/19/2001	Heather J. Belmont	49663 (71758)	2636

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/024,648	BELMONT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47 and 112-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47 and 112-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/22/09 has been entered. Applicant's amendment and response also received on 1/22/09 has been entered. Claims 3, 8-29, 32-37, 40, 46, and 48-111 are canceled. Claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-118 are pending and currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

It is again noted that claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-118 continue to read broadly on any non-human transgenic animal. The claims have been and continue to be examined in view of the elected subject matter, i.e. a transgenic mouse. It is further noted that the species of mouse was elected **without** traverse, and that neither the elected species nor the generic claims are found to be allowable.

Claim Rejections - 35 USC § 103

The rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-118 under 35 U.S.C. 103(a) as being unpatentable over U.S. 5,859,312 (1/12/99), hereafter referred to as Littman et al.

in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240, is maintained over claims 1-2, 4-7, 30-31, 38-39, 41-47, 112-113, and 116-118, and withdrawn over amended claims 114-115 in view of the added limitation that the human TCR alpha locus present in the transgenic animal contains all of the human TCR alpha V region, J region, and C region genes. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicants reiterate their previous arguments that none of the cited references provide the requisite teaching of a mouse comprising human TCR loci that are capable of undergoing productive rearrangement, or a reasonable expectation of success in producing such as mouse based on differences between the TCR gamma/delta versus TCR alpha/beta development and IgG heavy and light chain gene rearrangement and B cell development versus TCR alpha and beta chain gene rearrangement and T cell development. In addition, the applicant again argues that the constructs taught by McMurry et al. were designed with mutated V gene segments such that the rearranged TCR transgene does not express functional TCR protein products. Applicants interpret this decision to mutate the TCR loci as a sign that the authors of McMurry et al. were concerned that a productively rearranged human TCR would somehow interfere with normal T cell development.

In response, the previous office action stated that contrary to applicant's assertions, B cell development and T cell development are remarkably similar. Hardy et al., cited in the previous office action cited as rebuttal evidence in response to applicant's previous submission of

Sleckman and Kruisbeek, teaches that the various stages of B cell development parallel to a large degree those of T cell development as set forth in Kruisbeek et al. Pre-B cells rearrange the Ig heavy chain locus and express a pre-B cell receptor comprising the rearranged Ig heavy chain and a lambda 5/VpreB surrogate light chain just as T cells rearrange the TCR beta locus and express a pre-T cell receptor comprising the rearranged TCR beta chain and pTalpha/ VpreT surrogate alpha chain (Hardy et al. (2001) Annu. Rev. Immunol., Vol. 19, 595-621, see pages 599-600, and Kruisbeek et al., page 639, Figure 2). Signaling through each of these pre-receptors results in both cessation of further rearrangement of the heavy chain or beta chain resulting in allelic exclusion, and maturation to the next stage of B or T cell development, which is the rearrangement of the Ig light chain loci or the TCR alpha locus (Hardy et al., pages 600-601, Kruisbeek et al., page 637, and Sleckman et al., page 1465). Further stages in development are likewise similar, including positive and negative selection of B and T cells. Note that "similar" does not mean "identical" since clearly rearrangement of Ig loci and TCR loci is cell specific. However, applicant's reiteration of their argument that there is nothing in the transgenic IgG mouse literature to teach or suggest that an unrearranged human TCR beta locus could generate a functional human TCR beta chain to permit proper T cell development and T cell maturation is not persuasive as the evidence of record as discussed in previous office actions shows that at the time of filing human unrearranged Ig heavy chain loci were fully capable of productive rearrangement in mice and that functional, fully developed B cells expressing human Ig and capable of responding normally to antigen stimulation were produced in these mice. Such, evidence shows that clearly the human Ig heavy chain at the pre-B cell stage was capable of forming a functional complex with lambda 5 and VpreB to allow development beyond the pre-B

cell stage. In addition, regarding supposed differences between rearrangement of the delta locus versus the beta locus or the alpha locus versus the gamma locus, Lauzurica and Krangel teach that the same machinery is responsible for rearrangement of the gamma and delta loci as for the alpha and beta loci (Lauzurica and Krangel (1994), abstract). Furthermore, contrary to applicant's position that the skilled artisan would not have predicted that a productively rearranged human TCR would develop normally in the mouse, the prior art in fact teaches that transgenic mice comprising a rearranged human TCR beta transgene produced mature T cells expressing TCR comprising the recombinant human TCR chain which had successfully passed through positive and negative selection and were capable of mounting proliferative response to antigen (Rothe et al. (1993) Int. Immunol., Vol. 5(1), 11-17 –cited by applicant in IDS of 5/16/05, and Viney et al. (1992) Hybridoma, Vol. 11(6), 701-713- cited by applicant in IDS of 5/16/05). Thus, based on the state of the art at the time of filing, the clear parallels and similarities between B cell and T cell development as discussed above, and the evidence in the prior art that human TCR beta chains can signal properly in mice and participate in positive and negative selection, it is maintained that the skilled artisan would in fact have had a reasonable expectation that transgenic mice comprising unrearranged TCR beta and alpha loci would in fact be capable of rearranging these loci appropriately and further capable of developing mature T cells expressing functional alpha/beta TCR. The applicant is reminded that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell,* 7 USPQ2d 1673 (CAFC 1988).

In addition, regarding the teachings of McMurry, it is first noted that this reference was cited to support the teachings of Littman et al. and to provide evidence that human TCR genes can rearrange in mouse T cells using the endogenous mouse recombination machinery. McMurry et al. does not teach and was not cited for teaching any effect of the expression of functional human delta chains on T cell development in the mouse. As for the reasoning behind the mutation in the delta locus in the transgenic mice of McMurry et al., the previous office action discussed the fact that the original Lauzurica and Krangel publication in 1994, which gives the first description of the transgenic mice comprising a human TCR delta locus used by McMurry, specifically states the reason why the mutations to the V gene segments in the construct were added. On page 45, under the heading "strategy", the authors state, "[w]e wanted the construct to serve as an innocuous reporter that would not influence the rearrangement of endogenous TCR genes via the process of allelic exclusion" (Lauzurica and Krangel (January, 1994), Vol. 179, 43-55- page 45). Contrary to applicant's arguments, McMurry, as evidenced by the original Lauzurica and Krangel paper published in January of 1994 cited in McMurry et al., does not teach or suggest the expression of a human TCR would negatively influence thymic development. A second reference by Lauzurica and Krangel cited by applicants cited by applicant was not provided for the examiner's consideration. As noted in previous actions, the authors of Lauzurica and Krangel (January 1994) and McMurry et al. were originally trying to answer the question of whether some precommitment to the alpha/beta or gamma/delta cell lineage dictates gene rearrangement or whether gene rearrangement dictates cell lineage development. In the context of the question the authors were trying to answer, having the human delta chain functionally rearrange such that the protein was expressed would complicate the

situation since the human delta loci was intended to function as a marker for recombination so that the authors could observe recombination at this delta loci in both alpha/beta and gamma/delta lymphocytes. Thus, if rearrangement of the human delta loci was observed in alpha/beta T cells, this would support the gene rearrangement rather than precommitment theory. Since the authors felt the need to prevent functional rearrangement of the human delta loci, it must have been the authors expectation or prediction that productively rearranged TCR delta could affect allelic exclusion of the endogenous mouse loci which would skew their results. Since none of the Lauzurica and Krangel or McMurry references were interested in T cell development beyond the stage of rearrangement of the loci, and since none of the references give any indication or evidence that human TCR expression might negatively affect T cell development, applicant's interpretation of the reasoning behind the mutation in the human delta loci in the transgenic mice of Lauzurica and Krangel and McMurry et al. is not found persuasive or reflective of the actual teachings of these references.

Finally, please note that claims 1-2, 4-5, 30-31, 38-39, 41-45, 47, and 112-115 as written do not recite any functional limitation for the transgenic mice other than that they produce functional heterologous T-cell receptors. McMurry et al. provides clear evidence that human TCR genes are capable of rearrangement in a mouse. That teachings, in combination with the teachings of Littman et al., and state of the art at the time of filing as discussed in detail above, provides the reasonable expectation that urearranged human T cell alpha and beta loci would productively rearrange and express functional TCR protein in mice.

Therefore, for reasons of record and the discussion above, the rejection stands.

Applicant's amendment to the claims has necessitated the following new grounds of rejection under 35 U.S.C. 103(a).

Claims 114-115 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240 as applied to claims 1-2, 4-7, 30-31, 38-39, 41-47, 112-113, and 116-118 above, and further in view of the NCBI database Accession Number NG_001332.

Claims 114-115 as amended now recite the limitation that the human TCR alpha locus contains all of the human TCR alpha V, J, and C region genes, and that the human TCR beta locus contains all of the human TCR beta, V, D, J, and C region genes.

The teachings of Littman et al. in view of Mombaerts et al., McMurry et al., Rowen et al., and Rack et al. were set forth in the office action of 6/3/05. They are reproduced below for clarity of prosecution.

Littman et al. teaches general methods for producing transgenic non-human animals, preferably mice, which express human lymphocyte transduction proteins and lack expression of the cognate murine lymphocyte transduction protein as a result of inactivation of the endogenous lymphocyte transduction gene loci (Littman et al., abstract, columns 4-6). Littman et al. further teaches that the lymphocyte transduction gene loci and lymphocyte transduction genes include the T cell receptor genes and particularly the T cell receptor alpha and beta gene products (Littman et al., columns 8-9). Littman et al. further provides substantial guidance for making

transgenic mice which comprise human lymphocyte transduction transgenes in their genome and which have inactivated cognate lymphocyte transduction transgenes (Littman et al., columns 14-36).

Littman et al. differs from the instant invention by not specifically describing a transgenic mouse in which the TCR loci are inactivated and human unrearranged TCR V, D and/or J, and C genes have been inserted into the genome. It is noted that although Littman et al. suggests and provides motivation for inactivating the TCR loci of mice and inserting human TCR loci, Littman et al. exemplifies CD4 loci, not TCR loci. However, at the time of filing, transgenic mice which expressed unrearranged human T cell receptor loci and mice with have deletions in the endogenous TCR loci were described and available. Mombaerts et al. for instance teaches 3 different strains of mice which have inactivating deletions in the TCR alpha loci, TCR beta loci, or TCR delta loci (Mombaerts et al., page 275). In particular, note that Mombaerts teaches deleting the D,J, and C genes of the endogenous TCR beta locus (Mombaerts et al., page 3085, Figure 1). Mombaerts et al. also teaches double knock-out mice produced by crossing TCR beta and TCR delta knock-out mice (Mombaerts et al., page 275). McMurry et al. further supplements Littman et al. by teaching transgenic mice carrying the human unrearranged TCR delta gene minilocus. McMurry et al. teaches that the human TCR delta gene minilocus comprises unrearranged human multiple V, D, J, and C gene segments (McMurry et al., page 4553-4554). McMurry et al. also teaches that these mice are capable of successfully rearranging the human TCR delta gene locus. In addition, Rowen et al. and Rack et al. supplement the teachings of Littman et al. by teaching the complete 685-kB DNA sequence of the human beta TCR locus and a YAC containing 70% of the TCR alpha locus including multiple TCR alpha V genes, all of the

J genes and the C alpha gene respectively (Rowen et al., page 1755-1756, and Rack et al., page 1233-1234 and Figure 1). Further, although the YAC exemplified by Rack included only 70% of the TCR alpha locus, the entire human TCR alpha/delta locus present on chromosome 14 had been sequenced and mapped and was publicly available through the NCBI database.

Therefore, based on teachings and motivation provided by Littman et al. for making transgenic mice which contain human lymphocyte transduction loci, such as the TCR alpha and beta loci, and in which the endogenous lymphocyte transduction loci is inactivated, the teachings of Rowen et al., Rack et al., and the NCBI database that nucleic acids encoding the complete unrearranged human TCR alpha and beta loci were well known, and the teachings of McMurry et al. that transgenic mice comprising unrearranged human TCR loci could be effectively produced and that the human TCR loci were capable of successful rearrangement in mice, it would have been *prima facie* obvious to the skilled artisan to use the nucleic acids taught by Rowen et al. and Rack et al. to make transgenic mice as suggested by Littman et al. and to breed these transgenic mice with any of the TCR loci knock-out mice taught by Mombaerts et al. in order to produce a transgenic mouse in which the endogenous TCR alpha, and/or beta, and/or delta loci are inactivated and which contain the unrearranged human TCR alpha and beta loci. Further, based on the substantial direction provided by all of Littman et al., Mombaerts et al., and McMurry for making transgenic and knock-out mice, the successful demonstration by McMurry et al. that transgenic mice comprising unrearranged human TCR loci can properly rearrange the human loci, the high level of skill in breeding and crossing mice, and the state of the art at the time of filing, one of ordinary skill in the art would have had a reasonable expectation of success in

making a transgenic mouse comprising an inactivated endogenous TCR loci and comprising the complete human unrearranged TCR alpha and beta loci.

Please note that applicant's arguments regarding the teachings of Littman et al., Mombaerts et al., McMurry et al., Rowen et al., and Rack et al. were addressed in detail above and were not found persuasive. Applicant's further argument that none of these references teaches the complete human TCR alpha locus including all the V, J, and C region genes is also not persuasive as the complete human TCR alpha locus located on chromosome 14 had been sequenced and mapped and was publicly available at the time of filing, see the NCBI database.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the new technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the

USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633